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EXAMINER

MYERS, CARLA J

ART UNIT

PAPER NUMBER

1634

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23

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/037,472

Applicant(s)

DUFF, GORDON W.

Examiner

Carla Myers

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 28 August 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-17 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-17 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: _____ |

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1. The request filed on August 28, 2002 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/037,472 is acceptable and a CPA has been established. An action on the CPA follows.
2. Receipt is acknowledged of the Declaration signed by Ian G. Rennie, filed on April 16, 2001. However, the Declaration does not contain the signatures of inventors Patrick Richardson or Gordon Duff. Accordingly, a new oath or declaration signed by Patrick Richardson and Gordon Duff is required which claims priority to GB 9621129.7.
3. Claims 4-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for predicting a predisposition to clinically significant macular edema by detecting the presence of a genotype selected from the group consisting of (a) IL-1A (-889) 2,2 and IL-1B (-511) 2,2; (b) IL-1A (-889) 1,2 and IL-1B (-511) 2,2; and (c) IL-1A (-889) 2,2 and IL-1B (-511) 1,2, and methods for predicting a patient's predisposition to proliferative diabetic retinopathy wherein the presence of IL-1RN (VNTR) 2,2 is indicative of a decreased likelihood that the patient is predisposed to proliferative diabetic retinopathy, does not reasonably provide enablement for methods which detect the presence of IL-1 RN (VNTR) alleles as indicative of any disease other than proliferative diabetic retinopathy, methods which detect the presence of the IL-1A and IL-1B alleles as indicative of any disease other than clinically-significant macular edema, methods which detect polymorphisms other than IL-1A (-889), or IL b(-511) or IL-1RN (VNTR) or methods which identify polymorphism patterns in "other genes associated with sight-threatening diabetic retinopathy". The specification does not

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enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The specification has identified three alleles in the IL-1 gene cluster that are useful for predicting a patient's increased susceptibility to different forms of sight-threatening diabetic retinopathy. In particular, the specification teaches that the presence of IL-1 RN (VNTR) allele 2, 2 provides a protective effect against the development of proliferative diabetic retinopathy (see page 15 of the specification). No protective effect was found in patients which possess only one IL-1RN (VNTR) allele 2. The specification (page 16) also teaches that there is an increase risk of developing clinically-significant macular edema in diabetic patient's possessing one of the following genotypes: (a) IL-1A (-889) 2,2 and IL-1B (-511) 2,2; (b) IL-1A (-889) 1,2 and IL-1B (-511) 2,2; or (c) IL-1A (-889) 2,2 and IL-1B (-511) 1,2. Accordingly, the specification has enabled methods for predicting a patient's predisposition to proliferative diabetic retinopathy wherein the presence of IL-1RN (VNTR) 2,2 is indicative of a decreased likelihood that the patient is predisposed to proliferative diabetic retinopathy and methods for predicting a predisposition to clinically significant macular edema by detecting the presence of a genotype selected from the group consisting of (a) IL-1A (-889) 2,2 and IL-1B (-511) 2,2; (b) IL-1A (-889) 1,2 and IL-1B (-511) 2,2; and (c) IL-1A (-889) 2,2 and IL-1B (-511) 1,2.

The specification is not enabling for methods which detect alleles other than the IL-1B (-511) allele 2, IL-1A (-889) allele 2 or IL-1RN (VNTR) allele 2 polymorphisms because the specification has not taught any additional alleles that are associated with different forms of

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sight-threatening diabetic retinopathy and it is highly unpredictable as to what other alleles in the IL-1 gene cluster or what other genes in general contain alleles associated with sight-threatening diabetic retinopathy. There is no universal association between the presence of alleles in the IL-1 gene cluster and the occurrence of sight-threatening diabetic retinopathy. The art has not established a correlation between any alleles of IL-1 and the occurrence of disease which would allow for a general relationship to be established between the presence of an IL-1 gene cluster allele and sight-threatening diabetic retinopathy. The specification has not taught any particular attribute of the IL-1 RN (VNTR) allele 2, or IL-1B (-511) allele 2 or IL-1A (-889) allele 2 that could be extrapolated to other alleles in order to predictably identify other alleles in these genes and other IL-1 genes or any other unstated gene which would be predictive of sight-threatening diabetic retinopathy. Accordingly, there is no predictable means for determining which of the multitude of known and unknown alleles of IL-1 genes and other genes would be associated with sight-threatening diabetic retinopathy. Additional polymorphisms could only be identified by one of skill in the art through extensive trial and error experimentation. In addition, with respect to claim 9, the specification has not identified a single non-interleukin gene which is associated with sight-threatening diabetic retinopathy and has not provided sufficient guidance to enable one of skill in the art to predictably identify "DNA genetic polymorphism patterns for other genes associated with sight-threatening diabetic retinopathy". Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d

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1557, 1561. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that “(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art”. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that “(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement”. In the instant case, the specification has identified only the IL-RN (VNTR) 2,2 allele as being correlated with proliferative diabetic retinopathy and haplotypes of IL-1A and IL-1B carrying at least 3 copies of allele 2 of these genes as being associated with clinically-significant macular edema. Thereby, the scope of the claims does not bear a reasonable correlation to the scope of enablement provided by the specification and undue experimentation would be required to practice the full scope of the claims because this would require randomized searching of IL-1 genes and the entire genome for additional alleles which may be analyzed for their association with sight-threatening diabetic retinopathy. While it may be obvious to try to search for additional polymorphisms correlated with this disease and while it is within the skill of the art to detect sequence variations in general, it is highly unpredictable as to which other, if any, polymorphisms in unspecified known and unknown genes would be correlated with different forms of sight-threatening diabetic retinopathy. The methodology as defined in claim 9 in which polymorphisms are identified in IL-1A, IL-1B and IL-1RN genes, polymorphisms are identified in “other genes associated with sight-threatening diabetic retinopathy” and then a multiple genetic polymorphism pattern is developed and used to

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determine risk of sight-threatening diabetic retinopathy is considered to be a research project, rather than a methodology that allows one of skill in the art to determine a patient's risk of developing sight-threatening diabetic retinopathy without undue experimentation. The specification does not teach what number of polymorphisms must be carried by a patient in order to determine that the patient has an increased or decreased risk of developing or having sight-threatening diabetic retinopathy. The specification does not exemplify or describe any particular "multiple genetic polymorphism patterns associated with risk of sight threatening diabetic retinopathy" and does not provide sufficient guidance as to how to identify such multiple patterns without extensive experimentation. Furthermore, the specification has established specific correlations between IL-1RN (VNTR) allele 2,2 patterns and proliferative diabetic retinopathy and IL-1A (-889) and IL-1B(-511) allele 2 patterns and clinically-significant macular edema, but has not established a general correlation between IL-1RN (VNTR) polymorphisms or IL-1A/IL-1B genotypes and other types of diabetic retinopathy. The specification has not provided any data regarding the occurrence of these IL-1RN and clinically-significant macular edema or the occurrence of IL-1A/ IL-1B genotypes and proliferative diabetic retinopathy and has not established that polymorphisms associated with clinically-significant macular edema are also associated with proliferative diabetic retinopathy and vice versa. Accordingly, in view of the lack of information provided in the specification as to how to reasonably identify other alleles without undue experimentation and in view of the unpredictability in the art in correlating the presence of an allele with a disease, particularly in correlating the presence of an IL-1

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polymorphism with sight-threatening diabetic retinopathy, the specification has not adequately taught one of skill in the art how to practice the claimed invention as it is broadly claimed.

In the response of Paper No. 22, Applicants state that this rejection has been overcome by the amendment to the claims and that the preliminary amendment contains new claims which obviate the pending rejections. Applicants arguments and amendment have been fully considered but are not sufficient to overcome the present grounds of rejection for the following reasons. Firstly, it is noted that claim 9 does not recite any particular alleles for IL-1RN, IL-1A or IL-1B. Secondly, Claim 9 also requires identifying the genetic polymorphism pattern for “other genes associated with sight-threatening diabetic retinopathy”. However, as discussed in the above rejection, the specification has not identified any additional genes associated with sight-threatening diabetic retinopathy and undue experimentation would be required to identify additional genes and polymorphisms within these genes that are correlated with sight-threatening diabetic retinopathy. Thirdly, the rejection is based on the finding that the specification is enabling for methods for predicting a predisposition to clinically significant macular edema by detecting the presence of a genotype selected from the group consisting of (a) IL-1A (-889) 2,2 and IL-1B (-511) 2,2; (b) IL-1A (-889) 1,2 and IL-1B (-511) 2,2; and (c) IL-1A (-889) 2,2 and IL-1B (-511) 1,2, and for methods for predicting a patient’s predisposition to proliferative diabetic retinopathy wherein the presence of IL-1RN (VNTR) 2,2 is indicative of a decreased likelihood that the patient is predisposed to proliferative diabetic retinopathy. The specification has not established that all forms of sight-threatening diabetic retinopathy are associated with the

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presence of IL-1A (-889), IL-1B (-511) or IL-1RN VNTR, nor has the specification established that the presence of any single allele of the stated alleles alone (e.g., detection of IL-1A (-889) 1, 2 alone) can be used to detect sight-threatening diabetic retinopathy. Rather, the specification has established only that the combination of alleles of IL-1A (-889) 2,2 and IL-1B (-511) 2,2; (b) IL-1A (-889) 1,2 and IL-1B (-511) 2,2; and (c) IL-1A (-889) 2,2 and IL-1B (-511) 1,2, are correlated with significant macular edema and that the presence of IL-1RN (VNTR) 2,2 is correlated with decreased risk of developing proliferative diabetic retinopathy. For the reasons stated in the above rejection, it is unpredictable as to whether other forms of sight-threatening diabetic retinopathy would be associated with any combination of the IL-1A (-889), IL-1B (-511) or IL-1RN VNTR alleles and undue experimentation would be required to practice the invention as it broadly claimed.

4. Claims 7-10, and 12 and newly added claims 13 and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 7, 8, 10 and 12 are indefinite and confusing over the recitation of “presence at the combined loci of IL-1A plus IL-1B of at least three copies of the rarer allele for each loci (allele 2) between the two loci”. The claims should be amended to clearly set forth a Markush group listing the possible combined IL-1A and IL-1B patterns, e.g. “wherein said polymorphism pattern is selected from the group consisting of (a) IL-1A (-889) 2,2 and IL-1B (-511) 2,2; (b) IL-1A (-889) 1, 2 and IL-1B (-511) 2, 2; and (c) IL-1A (-889) 2,2 and IL-1B (-511) 1,2.

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Claim 9 is indefinite and vague over the recitation of “determining the number of polymorphisms” and “identifying diabetic patients expressing a multiple genetic polymorphism pattern” because the claim does not clearly state what constitutes a multiple genetic polymorphism pattern and this phrase is not defined in the specification and there is no statement in the claims as to what number of polymorphisms would be required to determine whether the patient was at risk of having sight-threatening diabetic retinopathy. While the specification exemplifies a pattern with 3 alleles at IL-1A (-889) and IL-1B (-511), the claims are not limited to this particular pattern. Rather, the claims include patterns obtained at any IL-1A, IL-1B and IL-1RN gene and any other genes associated with sight-threatening. The claims do not recite a particular number of polymorphisms or the identity of the polymorphisms that constitute the “multiple genetic polymorphism pattern associated with risk of sight-threatening diabetic retinopathy”.

NEW GROUNDS OF REJECTION:

Claims 13 and 15 are indefinite and vague because the method steps set forth in the claim do not agree back with and accomplish the objective set forth in the preamble. For example, claim 13 is drawn to a method for predicting an increased risk of familial sight-threatening diabetic retinopathy. However, the claim recites only a step of detecting the presence of allele 2 of IL-1A (-889) and allele 2 of IL-1B (-511). The claim does not set forth the relationship between detecting these alleles and predicting an increased risk of familial sight-threatening diabetic retinopathy. Therefore, it is unclear as to whether the method is intended to be limited

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to one for predicting an increased risk of familial sight-threatening diabetic retinopathy or one for detecting the presence of allele 2 of IL-1A (-889) and allele 2 of IL-1B (-511). Similarly, it is unclear as to whether claim 15 is intended to be limited to one for predicting a decreased risk of familial sight-threatening diabetic retinopathy or one for detecting the presence of allele 2 of IL-1RN (VNTR).

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 2 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mansfield (Gastroenterology (1994) 106:637-642) .

The claims are drawn to kits for identification of a patient's genetic polymorphism pattern. However, it is noted that in claims to products, such as kits, the intended use of the product does not carry weight with respect to the obviousness of the product.

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Mansfield teaches methods for detecting polymorphisms at position -511 of the IL-1B gene and at position -889 of the IL-1A gene and for detecting VNTR alleles of IL-1 RN. In the method disclosed by Mansfield, PCR is performed using primers complementary to sequences flanking the -511 allele of IL-1B which consist of the same sequences as instant SEQ ID NO: 3 and 4, primers complementary to sequences flanking the -889 allele of IL-1A which consist of the sequences identical to instant SEQ ID NO: 9 and 10 and primers complementary to sequences flanking the VNTR allele of IL-1 RN which consist of sequences identical to instant SEQ ID NO: 5 and 6 (see Table 2). The method of Mansfield further requires the use of reagents for performing PCR including a means for collecting DNA, DNA amplification means and a DNA detection means. Accordingly, Mansfield teaches a method which requires the use of reagents for the primers of SEQ ID NO: 1, 2, 3, 4, 9 and 10, DNA collection means and DNA amplification means. Mansfield does not teach packaging these reagents into a kit. However, reagent kits for performing DNA detection assays were conventional in the field of molecular biology at the time the invention was made and therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the primers and DNA collection means required to practice the method of Mansfield into a kit for the expected benefits of convenience and cost-effectiveness for practitioners of methods for detecting IL-1 RN (VNTR), IL-1A (-889) and IL-1B (-511) polymorphisms. With respect to claim 1, the amplification reagents, such as polymerase, disclosed by Mansfield are considered to be a means for determining the genetic polymorphism pattern for IL-1A (-889), IL-1B (-511) and

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IL-1RN (VNTR) because the amplification reagents allow for the amplification of sequences containing the stated polymorphisms. Thereby, the kits suggested by Mansfield containing DNA sample collection means and amplification reagents meets the limitations of claim 1.

It is noted that in claims to products, such as kits, the intended use of the product does not carry weight with respect to the obviousness of the product. As stated in MPEP 211.02, "When the claim is directed to a product, the preamble is generally nonlimiting if the body of the claim is directed to an old composition and the preamble merely recites a property in the old composition. *Kropa v. Robie*, 187 F.2d at 152, 88 USPQ at 480-481". The MPEP (2112) further states that "the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable".

6. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mansfield in view of Kornman (U.S. Patent 5,686,246).

Mansfield teaches methods for detecting polymorphisms at position -511 of IL-1B and at position -889 of IL-1A and for detecting VNTR alleles of IL-1 RN. In the method disclosed by Mansfield, PCR is performed using primers complementary to sequences flanking the -511 allele of IL-1B which consist of the same sequences as instant SEQ ID NO: 3 and 4, primers complementary to sequences flanking the -889 allele of IL-1A which consist of the same sequences as instant SEQ ID NO: 9 and 10 and primers complementary to sequences flanking the VNTR allele of IL-1 RN which consist of the same sequences as instant SEQ ID NO: 5 and 6 (see Table 2). The method of Mansfield also requires the use of reagents required to perform

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PCR including a means for collecting DNA, DNA amplification means and a DNA detection means. Mansfield (page 639) further teaches that the IL-1A (-889) polymorphism may be detected by restriction enzyme digestion with *NcoI* and the IL-1B (-511) polymorphism may be detected by restriction enzyme digestion with *AvaI*. Mansfield does not teach detecting the IL-1B (-511) polymorphism using the restriction enzyme *Bsu36I* and does not teach packaging the reagents required to detect the polymorphisms into a kit.

However, Kornman (col. 6) teaches that the IL-1B (-511) polymorphism may be detected using the restriction enzyme *Bsu36I* and specifically teaches that allele 2 of IL-1B (-511) contains a complete *Bsu36I* site. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Mansfield so as to have also detected allele 2 of the IL-1B (-511) polymorphism by digestion with *Bsu36I* because Kornman teaches that this is an effective means for directly detecting the presence of IL-1B (-511) allele 2. The resulting modified method of Mansfield thereby requires the use of reagents for collecting a DNA sample, the primers of SEQ ID NO: 1, 2, 3, 4, 9 and 10, and the restriction enzymes *NcoI*, *AvaI* and *Bsu36I*. In view of the conventionality of reagent kits for performing DNA detection, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the DNA collection means, restriction enzymes and primers required to practice the method of Mansfield into a kit for the expected benefits of convenience and cost-effectiveness for practioners of methods for detecting IL-1 RN (VNTR), IL-1A (-889) and IL-1B (-511) polymorphisms.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703)-308-1152. The fax number for the Technology Center is (703)-305-3014 or (703)-305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Carla Myers

October 28, 2002


CARLA J. MYERS
PRIMARY EXAMINER